

WHAT IS CLAIMED IS:

1. A method of enhancing the ability of a genotype 2b NS5B sequence to function in a replicon comprising the step of altering either, or both

5 (a) said genotype 2b NS5B sequence to encode one or more adaptive mutations selected from the group consisting of:

serine corresponding to position 24 of SEQ ID NO: 1;

isoleucine corresponding to position 31 of SEQ ID NO: 1;

leucine corresponding to position 392 of SEQ ID NO: 1; or

10 (b) a genotype 1b NS4B sequence to encode an adaptive mutation of alanine corresponding to position 218 of SEQ ID NO: 38.

2. The method of claim 1, wherein altering said genotype 2b NS5B sequence comprises at least isoleucine corresponding to position 31 of SEQ ID NO: 1, or at least serine
15 corresponding to position 24 of SEQ ID NO: 1 in combination with leucine corresponding to position 392 of SEQ ID NO: 1.

3. The method of claim 2, wherein said genotype 2b NS5B sequence is obtained from a clinical isolate.

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4. A method of producing a chimeric replicon comprising the step of replacing substantially all of a NS5B sequence of a HCV replicon comprising a NS3-5B genotype 1b sequence of encoding SEQ ID NO: 3, with a genotype 2b NS5B encoding nucleic acid sequence.

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5. The method of claim 4, further comprising the step of enhancing the ability of said genotype 2b NS5B according to the method of claim 1, wherein said enhancing can be done prior to, or after, said replacing step.

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6. The method of claim 5, wherein said genotype 2b NS5B sequence is obtained from a clinical isolate.

7. A chimeric replicon comprising:

35 a) a NS3-5A sequence of a genotype 1b replicon or a modified NS3-5A sequence of genotype 1b replicon wherein NS4B contains a V218A modification; and

b) substantially all of a genotype 2b NS5B encoding nucleic acid sequence.

8. The chimeric replicon of claim 7, further comprising a reporter or selection sequence.

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9. The chimeric replicon of claim 7, wherein said genotype 2b NS5B sequence encodes at least one of the following amino acids in the indicated position: serine corresponding to position 24 of SEQ ID NO: 1;

isoleucine corresponding to position 31 of SEQ ID NO: 1;

10. leucine corresponding to position 392 of SEQ ID NO: 1.

10. The chimeric replicon of claim 9, wherein said genotype 2b NS5B sequence encodes at least isoleucine corresponding to position 31 of SEQ ID NO: 1, or at least serine corresponding to position 31 of SEQ ID NO: 1 in combination with leucine corresponding to position 31 of SEQ ID NO: 1.

15. 11. The chimeric replicon of claim 8, wherein said genotype 2b NS5B sequence encodes NS5B provided by SEQ ID NO: 1.

20. 12. The chimeric replicon of claim 9, wherein said NS3-5A sequence consists of SEQ ID NO: 4 and NS5B sequence consists of SEQ ID NO: 2.

25. 13. The chimeric replicon of claim 12, wherein nucleotide 2711 of SEQ ID NO: 4 is C.

14. A recombinant cell comprising a replicon made the method of any one of claims 2-6, or the replicon of any one of claim 7-13, wherein said replicon is expressed in said cell.

30. 15. A method of measuring the ability of a compound to inhibit replicon activity comprising the steps of:

- a) providing said compound to the recombinant cell of claim 12, and
- b) measuring the ability of said compound to affect replicon activity.